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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/630,383	04/10/96	POULETTY	P A-55320-2/BI

HM12/0126

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EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
1644	29

DATE MAILED: 01/26/01

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Appl[illegible]
08/630,383	Pouletty et al.
Examiner	Group Art Unit
Ron Schwadron, Ph.D.	1644

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-11 and 13* is/are pending in the application.

Of the above, claim(s) 3, 5, 9-11, 13 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 2, 4, 6-8 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The request filed on 2/22/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/630383 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's election without traverse of Group I and the species G in Paper No. 26 is acknowledged.

3. Claims 13,3,5,9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions or species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 26.

4. Claims 1,2,4,6-8 are under consideration. The amendment filed 1/5/98 has been entered.

5. Claims 1,2,4,6-8 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

The specification does not disclose how to use the instant invention for the treatment of disease in vivo in humans. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification. See Ex parte Forman, 230 USPQ 546, BPAI, 1986. Regarding applicants comments, the following comments are made. Regarding applicants various comments about utility and the utility guidelines, applicant is reminded that no rejection under 35 U.S.C. §101 is present in the instant Office Action and that the rejection under consideration is under 35 U.S.C. § 112, first paragraph. The Official Gazette (1177 OG 146) states in column 1, third paragraph (under section I) that lack of a rejection under 35 U.S.C. §101 does not mean that a specification is therefore enabled under 35 U.S.C. §112, first paragraph. The claims of the instant invention read on a method that the specification discloses can be used for the treatment of human disease in vivo. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method for human therapy.

The state of the art is such that is unpredictable from the in vitro or in vivo mouse data disclosed in the specification as to whether (and how) the instant invention could be used for the treatment of disease in vivo in humans.

Regarding the mouse data disclosed in page 23 of the specification, said experiments relate to the lysis of normal cells and provides no evidence that the instant invention can be used for the treatment of any mouse disease. Regarding the mouse allograft data disclosed in page 30 of the specification, it is well known in the art that rodent models for the study of transplantation do not produce results that are readily applicable to humans and are therefore not predictive of whether particular agents can be used in vivo for the treatment of transplantation rejection in humans. Tueveson et al. teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in humans (see page 100, first full paragraph). Tueveson et al. also teach that, "However, today's small animal models seem to be insufficient to produce data for clinical decision-making." (page 101, second paragraph). Osband et al. teaches that the response of animals to immunotherapy is not predictive of the response in humans(see page 193, second column, first paragraph). The data disclosed in page 30 of the specification provides no evidence that naturally occurring endogenous antibodies (eg. autoantibodies, antibodies against xenoantigens), which are encompassed by the claims of the instant invention, can function as an effector mechanism in the claimed invention. Borrebaeck et al. teach that naturally occurring antibodies against xenoantigens(eg. anti α gal antibodies) do not function as an endogenous effector system as per the claimed method, for the reasons stated below (see comments about Borrebaeck et al.). The evidence of record has also provided no working examples demonstrating that the conjugates used in the method of the instant invention can used to reduce the concentration of a soluble target molecule.

Regarding the Soulillou declaration filed 3/31/97, no copy of Soulillou's curriculum vitae was submitted with the instant declaration, therefore, it is unclear as to whether Dr. Soulillou is an expert in the field of immunology. Furthermore, the Soulillou declaration provides no experimental evidence which establishes that the rodent models for the study of transplantation produce results that are readily applicable to humans and are therefore predictive of whether particular agents can be used in vivo for the treatment of transplantation rejection in humans. Tueveson et al. teach that one problem with rodent models of transplantation is that rejection is

easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in humans. The Soulillou declaration filed 3/31/97 does not provide any evidence that contradicts the aforementioned problem noted by Tueveson with regards to rodent models for transplantation. In fact, Soulillou seems to indicate that Tueveson et al. are correct in stating that there is no direct correlation between the rodent model and applicability to human use (eg. see first complete paragraph). The issue at hand is not whether the rodent model is used to screen for immunosuppressive drugs, but whether the rodent model is predictive in itself of whether an agent can be used in vivo for the treatment of human disease. Regarding Soulillou's comments on page 2, the murine and human immune systems differ in many ways. For example, the human immune system contains anti- α gal antibodies are not found in rodents and which can neutralize the efficacy of rodent antibodies. Regarding applicants comments about the Tueveson et al. publication, no actual evidence has been presented in the Soulillou declaration which refutes the statements made by Tueveson et al. Regarding comments about in the Soulillou declaration about Borrebaeck et al., Borrebaeck et al. teach that murine antibodies often contain the α gal antigen (see page 477). Borrebaeck et al. teach that naturally occurring anti-α gal antibodies are found in humans and that said antibodies bind murine monoclonal antibodies when said murine monoclonal antibodies are administered to humans (see page 477, third column first complete paragraph). Borrebaeck et al. teach that , "The presence of anti-Gal antibodies in human serum ensures a quick removal of the xenogeneic mouse mAbs, containing Gal α 1-3Gal residues, which results in a lack of antibody mediated effect on neoplastic target cells"(see page 477, third column first complete paragraph). It appears that conjugates containing α gal antigen would also suffer a similar fate and therefore also not be available to mediate lysis of a target cell. Borrebaeck et al. also teaches that the binding of anti-α gal antibodies interferes with the immune function of murine monoclonal antibodies without resulting in any effector function as a consequence of the bound anti-α gal antibodies (see page 477, third column, first complete paragraph, last sentence). The teachings of Borrebaeck et al. seem to indicate that the preformed antibodies (eg. endogenous antibodies) do not act as an immunologic effector system upon binding of said antibodies to an exogenously administered agent , but instead result in the removal of said agent thus preventing the agent from reaching the appropriate target cell. The Soulillou declaration has provided no actual evidence that contradicts the statement made by Borrebaeck et al.

With regards to the in vivo use of antibody containing conjugates, Waldmann teaches that

the therapeutic use of antibody treatment with any particular antibody/antibody conjugate in humans is unpredictable from in vitro data or in vivo animal data alone. Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. "(see page 1657, first column, last paragraph). Waldmann also states that results from clinical studies in humans using antibody based therapeutics for the treatment of cancer did not fulfill the hopes engendered by in vitro studies (see page 1660, second column, last paragraph). Waldmann teaches that the effectiveness of rodent monoclonal antibodies is limited because they "have a short survival time in humans and induce an immune response that neutralizes their therapeutic effect"(page 1658, second column, third paragraph). Waldmann teaches that even human antibodies can be immunogenic by virtue of their idiotypic elements(see page 1659, first column, lines 4 and 5). Harris et al. teach that, "There is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy" and goes on to list problems encountered upon the use of murine antibodies for human therapy (see page 42, second column, first paragraph). Harris et al. also states that, "However, the residual HAMA response to chimaeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective" (see page 42, third column). The Soulillou declaration has provided no actual evidence that contradicts the statement made by Waldmann or Harris et al. Regarding applicants comments, none of the claims under consideration recite the use of humanized monoclonal antibodies or that the host is immunosuppressed. No evidence has been presented indicating that murine monoclonal antibodies per se can be used for the treatment of human disease.

Regarding applicants comments, the claims of the instant invention do not specify that the target is T cells involved in transplantation rejection. The claims read on a method where the target could be a T cell lymphoma which expresses IL-2 receptors. In such a scenario, normal T cells capable of mediating killing would also express the IL-2 receptor, and therefore the aforementioned conjugate would bind to normal T cells and not be available to bind a target cell. Furthermore, the killing of normal T cells would leave tumor bearing patient immunocompromised without necessarily having any effect on the T cell lymphoma. This would also apply to many cytokines, whose receptors are also found on T cells (such as IL-4, IL-6, IL-10, etc.).It is unclear as to how the method of the instant invention can inactivate target cells without also inactivating normal cells that express receptors for said cytokine. If the target cell

population is present in lesser numbers compared to normal cells which express the relevant cytokine receptor it is also unclear as to whether sufficient quantities of said conjugate would be present to react with a target cell population after interaction with normal cells that possess the pertinent cytokine receptor. Regarding applicants comments, there is no limitation in the claims that specifies that the target cell population has a surface membrane receptor that is upregulated in a particular population but not normal cells.

With regards to claims that read on the use of α gal containing conjugates in mammals, anti α gal endogenous antibodies are not found in mammals per se, but only in humans and old world monkeys (see Borrebaeck et al., column 1, first indented paragraph). Therefore said conjugates could not be used in mammals per se.

In addition, there is no guidance in the specification as to how to determine the dosage of conjugate to use for treatment of a particular disease. It is therefore unclear as to whether the dosages used in said experiment could be used for the treatment of disease, because no disease was actually treated in said experiment. There is also no evidence of record that establishes that the mouse pharmacokinetic response to the conjugate would be the same as humans. Borrebaeck et al. establish that there are clear pharmacokinetic differences in the halflife of murine antibodies administered to mice versus humans, in that murine antibodies administered to humans have greatly reduced halflife in comparison to human antibodies (see column 1, page 477). Therefore a xenogeneic conjugate administered to a human would not necessarily have the same pharmacokinetic properties as when said conjugate was administered to a human. The Borrebaeck et al. reference establishes that conjugates containing α gal would be subjected to an anti-α gal response (that can neutralize the conjugate), wherein such a response would not occur in mice because anti-α gal antibodies are not found in mice. There is also no guidance in the specification as to how to determine if an appropriate level of endogenous antibody (eg. endogenous cytotoxic effector) is present so that target cell lysis could be effected by the administered conjugate.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use

or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1,2,6 stand rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Pouletty (EP 0510949) for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants comments, the Board of Appeals upheld the rejection of claims filed in 07/690530 as not enabled under 35 USC 112 first paragraph for the reasons disclosed in the Board decision mailed 9/30/99. Therefore, the claimed invention is not entitled to priority to parent application 07/690530 because the claimed invention was not enabled in said application.

In addition, regarding the limitation of claim 6, there is no disclosure in parent application 07/690530 of use of a "small organic molecule having a molcular weight of more than 100 and less than about 5000 daltons". Regarding applicants comments about page 4, lines 1-22 of 07/690530, said passage does not disclose a "small organic molecule having a molcular weight of more than 100 and less than about 5000 daltons" or the scope of said phrase. Applicant appears to be arguing that the limitation is obvious in view of a specific example disclosed in the specification, even though specific example does not provide written description of the scope of the claimed invention. However, obviousness is not the appropriate standard with regards to issues of written description. The CAFC stated in Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1997) that:

3. Patentability/Validity -- Specification -- Written description (§ 115.1103)
Patent's entitlement to earlier filing date extends only to that which is disclosed in prior application, and does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed; one shows that one is "in possession" of invention of patent by describing invention, with all its claimed limitations, not that which makes it obvious, and although prior application need not describe claimed subject matter in exactly same terms used in claims, prior specification must contain equivalent description of claimed subject matter, and description which renders obvious invention for which earlier filing date is sought is not

sufficient. The CAFC also stated in Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977) that:

The invention is, for purposes of the 'written description' inquiry, whatever is now claimed .") (emphasis in original). One does that by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention. Although the exact terms need not be used in haec verba , see Eiselstein v. Frank , 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (" [T]he prior application need not describe the claimed subject matter in exactly the same terms as used in the claims.. . . "), the specification must contain an equivalent description of the claimed subject matter. A description which renders obvious the invention for which an earlier filing date is sought is not sufficient.

8. Claim 1 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Kranz et al. (EP 0180171).

Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used does not use an antibody as the "moiety specific for a surface protein" (see abstract and claims). Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31) and a "selective moiety" which is an antiT3 antibody (which binds the TCR). The claims under consideration do not exclude use of an antibody as the "selective moiety". Kranz et al. disclose the claimed method is used in vivo wherein lysis is mediated by T cells which bind said conjugate wherein the conjugate is bound by the appropriate target cell (see pages 3 and 4).

9. Claims 1,2,6-8 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Pillai et al.

Pillai et al. teach in vivo administration of a conjugate containing Il-2 attached to a carbohydrate antigen (see column 3). The carbohydrate antigen is an antigen to which the host is previously sensitized (eg. one of the antigens disclosed in penultimate paragraph, column 3). While the reference does not disclose that the administration of the conjugate will lead to lysis of a target cell via the mechanism recited in the claim, said lysis will inherently occur because the claimed method recites the same steps as disclosed by Pillai et al. (eg. in vivo administration of the identical conjugate recited in the claims). Pillai et al. disclose that the conjugate is

administered to a "warm blooded animal" (eg. mammal, see column 4, last paragraph).

10. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claim 4 remains rejected under 35 U.S.C. § 103 as being unpatentable over Pouletty (EP 0510949) in view of prior art disclosed in the specification (page 9, first complete paragraph) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive. Regarding applicants arguments, while the claimed invention is obvious over the prior art, there is no disclosure of said invention in parent case 07/690530, thus, said invention does not receive priority to said application.

12. Claims 1,7,8 are rejected under 35 U.S.C. § 103 as being unpatentable over Kranz et al. in view of Park et al. (US Patent 5,298,395).

Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used does not use an antibody as the "moiety specific for a surface protein" (see abstract and claims). Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31) and a "selective moiety" which is an antiT3 antibody (which binds the TCR). The claims under consideration do not exclude use of an antibody as the "selective moiety". Kranz et al. disclose the claimed method is used in vivo wherein lysis is mediated by T cells which bind said conjugate wherein the conjugate is bound by the appropriate

target cell (see pages 3 and 4). Kranz et al. do not disclose use of a cytokine such as Il-2 as the "moiety specific for a surface protein". Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31). Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor (see column 3, first complete paragraph). Park et al. disclose use of the cytokine IL-2 in such conjugates (see column 4, first complete paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used contains a growth factor as the "moiety specific for a surface protein" (see claims 27-31) and a "selective moiety" which is an antiT3 antibody (which binds the TCR), while Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor. One of ordinary skill in the art would have been motivated to do the aforementioned because Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used contains a growth factor as the "moiety specific for a surface protein", while Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor.

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644
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